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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/375,924	08/17/1999	MICHAEL GALLO	ABGX-2-CIP	5797

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FISH & NEAVE
1251 AVENUE OF THE AMERICAS
50TH FLOOR
NEW YORK, NY 10020-1105

EXAMINER
JAMROZ, MARGARET E

ART UNIT	PAPER NUMBER
1644	25

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/375,924	GALLO ET AL.	
	Examiner	Art Unit	
	Margaret E Jamroz	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2002 and 15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18 & 20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Notice to comply with the Sequence Rules.

DETAILED ACTION

1. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Megan Jamroz, Art Unit 1644, Technology Center 1600.

2. The request filed on 2/15/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/375,924 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's amendment, filed 1/4/2002 (Paper No. 18), is acknowledged.

Claims 44-51 (previous claims 21-43) are pending and are under consideration in the instant application.

Sequence compliance

3. The specification is objected to under 37 CFR 1.821(d). This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded to amend the specification (including the Brief Description of Drawings) and claims as appropriate to reflect compliance with the Sequence Rules.

Specifically, for the two sequences disclosed in the specification on page 47, lines 14 and 18, applicant is required to provide SEQ ID NOS for the two sequences, a substitute paper copy of the "Sequence Listing", a substitute computer readable form (CRF) copy of the "Sequence Listing", and a statement that that the content of the paper and computer readable copies are the same, and where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

4. Applicant's IDS, filed 01/04/02 (Paper Nos. 18 and 20), are acknowledged, however, the references for the citations were crossed out were not found in the instant application. Applicant is invited to produce such documents. The examiner apologizes for an inconvenience to applicant in this matter.

In view of the amendment filed 01/04/2002 (Paper No. 18), only the following rejections remain.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 44-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 01/04/2002 have been fully considered but they are not persuasive.

Applicant's position is that:

(1) the argument set forth by the Examiner with respect to the *Regents of the University of California v. Eli Lilly and Co.* 43 USPQ2d 1398, at 1406, was improperly applied to the instant application as the instant claims are not drawn to genes;

(2) sufficient structural and functional attributes of the claimed antibodies have been provided; and

(3) the proper function of the invention is pH-dependent binding: modified antibodies of the instant invention bind FcRb receptor in the acidic environment of cellular endosomes (ca. pH 6.0), but are released when the FcRb receptor is again exposed to the slightly basic pH of the serum (ca. pH 7.4) (p. 28).

(1) It is the examiner's opinion with respect to the decision concerning the *Regents of the University of California v. Eli Lilly and Co.* 43 USPQ2d 1398, at 1406, that although the instant claims are not drawn to genes, the specification does not show that applicant is in possession of the genus of "moieties" wherein the antibody can be any isotype, such as IgA, IgM, IgE, IgD, or IgG3. The *Regents of the University of California v. Eli Lilly and Co.* 43 USPQ2d 1398, at 1406 has set forth the principle that disclosure of a single species or a few (in this case 3) species cannot read on a genus as broad as the genus of the claimed antibodies.

Applicant is only in possession of IgG1, IgG2, and IgG4 "moieties" capable of binding to a FcRb receptor in a pH dependent manner. Further, applicant has not shown possession of any immunoglobulin molecule wherein the antibody bind FcRb receptor with greater avidity at pH 7.4 after said linking.

In the instant application, applicant's amendment filed 8/22/2000 on page 11 at lines 27 and 28 and the footnote on page 12 is an admission that Applicant acknowledges the equivalence of the FcRp, FcRn, and RcRb receptors.

Applicant admits in the amendment filed 01/02/2002 on page 25, paragraph 2 and Appendix C: Table 4-2 is that Applicant acknowledges that it "is made clear by recitation, as examples of immunoglobulins, of IgA, IgD, IgE, and IgM, the immunoglobulin classes known not to bind FcRp, and therefore to have short serum half-lives.[21]". Applicant admits that "three of the four human IgG subclasses (i.e. IgG1, IgG2, and IgG4) bind FcRp"; see footnote 20 as well. Additionally, the last line of page 25 which wraps around to page 26, lines 1-2 and footnote 23 is applicant's admission that "Antibodies of the IgG3, subclass, in contrast, except for rare allotypes do not bind FcRp.[23]".

Consequently, the concept of species vs. genus as set forth by the *Regents of the University of California v. Eli Lilly and Co.* 43 USPQ2d 1398, at 1406 provides strong guidance as to applicant's lack of support for the genus of antibody molecules. Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all of the contemplated antibody "moiety" possibilities recited in the instant claims which are capable of performing the function of binding to FcRb receptors as broadly claimed.

Consequently, the Examiner's application of the decision by concerning the *Regents of the University of California v. Eli Lilly and Co.* 43 USPQ2d 1398, at 1406 was appropriate and correct.

In light of the above admissions, the decision by Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 has been correctly applied because the genus of antibodies with the function of binding to FcRb receptors is not supported by the disclosed structures of IgG1, IgG2, and IgG4 antibody moieties.

(2) With respect to applicant's opinion that a sufficient structural and functional description of the claimed antibody "moiety" has been provided, it is the examiner's position that applicant has not shown possession of the genus of antibody moieties as described above. The specification fails to show that IgA, IgM, IgE, IgD, or IgG3 can be used in the claimed invention; therefore, applicant is not in possession of the genus of antibody moieties as broadly claimed.

(3) The examiner's opinion applicant has pointed to page 28, lines 6-13 of the specification disclose that "Such modified molecules are expected to still bind in a pH dependent and biologically relevant manner (pH 6.0). Moreover, in molecules where the receptor binding domain itself remains unmodified, the ability of the modified molecule to dissociate from the receptor at neutral pH which is essential for recycling the antibody back to the plasma, should not be compromised".

It is the examiner's opinion that claim 44 recites wherein said antibody binds FcRb receptor with greater avidity at pH 7.4 after said linking; however, according to page 28, lines 1-6, the modified antibody dissociated from the receptor when the pH increases from 6.0 to a more neutral pH. The statements by the specification and the claim, therefore, are direct opposites. An antibody cannot bind with greater avidity when it is dissociated from its receptor.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in

possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following rejections are necessitated by the amendment filed 01/04/2002 (Paper No. 18).

6. Claims 44-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

Applicant's amendment asserts that no New Matter has been added. However, the specification and the claims as originally-filed do not provide a clear support for "wherein said antibody binds FcRb receptor with greater avidity at pH 7.4 after linking" (claim 44) or "wherein said at least second moiety confers upon said antibody avidity of binding FcRb receptor at pH 7.4 greater than that of said antibody lacking said at least second moiety" (claim 49).

In paragraph 2 of page 9 of the amendment filed 01/04/2002, Applicant points to page 3, lines 1-5; page 28, lines 6-13; page 53, lines 31-34; page 54, lines 16-21; and page 26, lines 4-24 as providing support for the above mentioned phrases.

Page 3, lines 1-5 of the specification discloses that "the interaction of IgG with the RcRb receptor is pH dependent (binding at pH 6.0 and dissociating at pH 7.0) has also been studied in some detail".

Page 28, lines 6-13 of the specification discloses that "Such modified molecules are expected to still bind in a pH dependent and biologically relevant manner (pH 6.0). Moreover, in molecules where the receptor binding domain itself remains unmodified, the ability of the modified molecule to dissociate from the receptor at neutral pH which is essential for recycling the antibody back to the plasma, should not be compromised".

Page 53, lines 31-34 of the specification discloses that "The highest expressers with be expanded and the secreted FcRp will be purified using pH-dependent binding to a rat IgG column".

Page 54, lines 16-21 of the specification discloses that "Cell lines that express the FcRp on their cell surface in a stable manner will be identified by incubating the cells at pH 6.0 with a FITC conjugated human IgG followed by analysis on FACS. Subsequent FACS analysis at both pH 6.0 and pH 7.4 will confirm that the binding is mediated by FcRp".

Page 26, lines 4-24 of the specification do not mention pH or avidity at al.

It is the examiner's opinion that none of the passages supplied by applicant provide support for "wherein said antibody binds FcRb receptor with greater avidity at pH 7.4 after linking" (claim 44) or "wherein said at least second moiety confers upon said antibody avidity of binding FcRb receptor at pH 7.4 greater than that of said antibody lacking said at least second moiety" (claim 49).

Applicant is required to cancel all new matter. Alternatively, applicant must point to more specific teachings in the specification to support the claimed subject matter.

7. Claims 44-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody with extended serum half-life having a first IgG1, IgG2, or IgG4 moiety capable of binding to FcRb receptor linked to a second IgG1, IgG2, or IgG4 moiety capable of binding to FcRb receptor in a pH-dependent manner, does not reasonably provide enablement for an antibody with extended serum half-life having a first moiety of any other isotype capable of binding to FcRb receptor linked to a second moiety of any other isotype capable of binding to FcRb receptor in a pH-dependent manner wherein said IgG3 binds with a greater avidity at pH 7.4 after said linking. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

The admission in Applicant's amendment filed 8/22/2000 on page 11 at lines 27 and 28 and the footnote on page 12 is that Applicant acknowledges the equivalence of the FcRp, FcRn, and RcRb receptors.

The admission in Applicant's amendment filed 01/02/2002 on page 25, paragraph 2 and Appendix C: Table 4-2 is that Applicant acknowledges that it "is made clear by recitation, as examples of immunoglobulins, of IgA, IgD, IgE, IgM, the immunoglobulin classes known not to bind FcRp, and therefore to have short serum half-lives.[21]". Applicant admits that "three of the four human IgG subclasses (i.e. IgG1, IgG2, and IgG4) bind FcRp"; see footnote 20 as well. Additionally, the last line of page 25 which wraps around to page 26, lines 1-2 and footnote 23 is applicant's admission that "Antibodies if the IgG3, subclass, in contrast, except for rare allotypes do not bind FcRp.[23]".

The specification has not provided any guidance as to how IgA, IgD, IgE, IgM, and IgG3 could be modified such that they would first, bind FcRb, FcRp, or FcRn, and second, if those modifications would be sufficient to cause the modified IgA, IgD, IgE, IgM, and IgG3 moieties to bind with greater avidity at pH 7.4 after said linking of the two moieties as claimed. Applicant has not provided any working examples of antibody moieties of IgA, IgD, IgE, IgM, and IgG3 isotypes and subclasses as claimed.

In view of applicant's admission that only human IgG1, IgG2, and IgG4 are capable of binding to FcRb, it is highly unpredictable that IgA, IgD, IgE, IgM, and IgG3 could be applied to the claimed invention, and it would require one skilled in the art an undue amount of trial and error to practice the invention as broadly claimed.

Further, in view of applicant's disclosure on page 28, lines 6-13 of the specification that "Such modified molecules are expected to still bind in a pH dependent and biologically relevant manner (pH 6.0). Moreover, in molecules where the receptor binding domain itself remains unmodified, the ability of the modified molecule to dissociate from the receptor at neutral pH which is essential for recycling the antibody back to the plasma, should not be compromised", it would take an undue amount of experimentation for one skilled in the art to show that avidity was greater at pH 7.4 after linking of two IgG1, IgG2, and IgG4 moieties when said moieties would have dissociated from the FcRb at a more neutral pH.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. No claim is allowed.

9. The drawings are objected to because of the errors listed on the PTO-948; therefore, the drawings fail to comply with 37 CFR 1.84.

The Patent and Trademark Office no longer makes drawing changes. See 1017 O.G. 4. It is applicant's responsibility to ensure that the drawings are corrected. Corrections must be made in accordance with the instructions below.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Megan Jamroz, whose telephone number is (703) 308-8365. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Margaret (Megan) Jamroz, Ph.D.
Patent Examiner
Technology Center 1600
May 1, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No.	Applicant(s)	
	09/375,924	GALLO ET AL.	
	Examiner	Art Unit	
	Margaret E Jamroz	1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Page 47, lines 14 and 18 contain sequences for primers which are not identified by a SEQ ID NO.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

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